Characteristics and Outcomes of Continuous Renal Replacement Therapy in Pediatric Sepsis: Report from the Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK)

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Introduction

Sepsis is common in the pediatric intensive care unit (PICU) and is associated with high morbidity and mortality.

- SPROUT: 10% prevalence of severe sepsis/septic shock, 30% of whom develop progressive multiple organ dysfunction and subsequent disability at discharge, with 25% suffering mortality
- LAPSE: 13% of children who survive their index admission for severe sepsis/septic shock die by 1 year following discharge, and 35% have not regained baseline health-related quality of life at that time

Acute kidney injury (AKI) is a common complication of pediatric sepsis that increases the risk of poor outcomes in these patients.

- 20-50% of children with severe sepsis/septic shock develop sepsis-associated AKI
- Severe sepsis-associated AKI has been demonstrated to be independently associated with greater odds of mortality and/or new disability.

Unfortunately, there are no disease-modifying therapies for sepsis-associated AKI once present, and thus providers are forced to rely on supportive care measures such as continuous renal replacement therapy (CRRT) to manage these children. Limited data exist regarding characteristics and outcomes of children with sepsis requiring CRRT.

Objectives:

1. To describe the characteristics and outcomes of children with sepsis requiring CRRT compared to those without sepsis.
2. To identify factors associated with the development of Major Adverse Kidney Events at 90 days (MAKE-90) in children with sepsis requiring CRRT.

Methods and Materials

Study Design: A secondary analysis of WE-ROCK, an international (9 countries), multicenter (34 centers), retrospective study of subjects aged 0-25 years treated with CRRT for AKI or fluid overload from 2015-2021.

Inclusion Criteria: Subjects from the original study were included in our secondary analysis if they had sepsis at CRRT initiation, which was defined as:

- ≥2 SIRS criteria
- Being treated for a known/suspected infection

Primary Outcome: The primary outcome of interest was the development of MAKE-90 in children with sepsis requiring CRRT, defined by the presence of any of the following at 90 days:

- Mortality
- Persistent kidney dysfunction (≥25% eGFR decline)
- RRT dependence

Secondary Outcomes:

- CRRT liberation by 28 days
- Total CRRT duration

Analyses:

- **Objective 1:** Demographic, clinical and outcome characteristics of subjects with sepsis (n=446) requiring CRRT were compared to those without sepsis (n=570) requiring CRRT.
- **Objective 2:** Univariate analysis was performed in patients with sepsis requiring CRRT who survived >48 hours comparing subjects who suffered MAKE-90 (n=260) versus those who did not (n=133). Multivariable logistic regression was then used to identify independent associations with MAKE-90 incorporating variables with $p<0.15$ on univariate analysis and adjusting for center using a mixed-effects model.

Results

Objective 1: Describe and compare characteristics and outcomes for children with sepsis requiring CRRT to those without sepsis requiring CRRT.

Characteristic	All (n=1016)	Sepsis (n=446)	No Sepsis (n=570)	p
Age, years	8.3 (1.6-15)	10.2 (2.3-15.4)	6.4 (1.3-14.5)	0.003
Sex, female	462 (45)	211 (47)	251 (44)	0.30
PRISM III	14 (10-18)	15 (11-20)	14 (9-18)	<0.001
Time from ICU Admit to CRRT, days	2 (1-6)	2 (1,7)	2 (1,6)	0.56
PELOD-2 at CRRT Initiation	5.0 (2.0-8.0)	7.0 (3.0-10.0)	5.0 (2.0-7.0)	<0.001
Pre-CRRT VIS	5 (0-20)	10 (0-30)	0 (0-13)	<0.001
% Fluid Balance at CRRT Initiation	8 (2-18)	10 (4-21)	6 (2-16)	<0.001
CRRT Modality at Initiation				0.21
CVVH	112 (11)	44 (9.9)	68 (12)	
CVVHD	114 (11)	43 (9.6)	71 (13)	
CVVHDF	767 (76)	353 (79)	414 (73)	
mCVVH	8 (0.8)	2 (0.4)	6 (1.1)	
SCUF	12 (1.2)	4 (0.9)	8 (1.4)	
Median CRRT Dose, ml/kg				
First 48 hours (Day 1-2)	43 (32-61)	44 (32-60)	43 (31-63)	0.61
First week (Day 1-7)	44 (32-63)	45 (33-60)	44 (32-66)	0.63
CRRT Liberation by Day 28, yes	349 (34)	134 (30)	215 (38)	<0.001
Total CRRT Duration, days	6 (3-14)	7 (4-15)	5 (3-13)	0.026
MAKE-90, yes	650 (64)	309 (70)	341 (61)	0.002
Mortality, yes	384 (38)	209 (47)	175 (31)	<0.001
Persistent kidney dysfunction, yes	173 (33)	76 (36)	97 (31)	0.22
RRT dependence, yes	93 (15)	24 (10)	69 (18)	0.011

Objective 2: Identify factors associated with MAKE-90 in children with sepsis requiring CRRT.

Variable	Univariate Analysis (n=393)			Multivariable Analysis (n=393)		
	MAKE-90 (n=260)	No-MAKE-90 (n=133)	p	aOR	95% CI	p
Age, years	11 (3-16)	7 (2-13)	0.03*	1.05	1.01-1.09	0.006
Baseline Serum Creatinine, mg/dl	0.40 (0.23-0.65)	0.48 (0.35-0.62)	0.04*	0.69	0.44-1.08	0.10
PRISM III	14 (11-19)	16 (11-21)	0.18			
PELOD-2 at CRRT Initiation	6 (3-10)	6 (3-8)	0.49			
VIS at CRRT Initiation	10 (0-26)	6 (0-27)	0.50			
Time from ICU Admit to CRRT, days	2 (1-8)	2 (1-4)	0.22			
%Fluid Balance from ICU Admit to CRRT	9 (4-20)	11 (4-24)	0.21			
Vasoactive Change 1st 48h CRRT			0.03*			
Never Required	51 (20)	30 (23)		--	--	--
Unchanged/Increased	62 (24)	17 (13)		0.93	0.39-2.22	0.87
Decreased	146 (56)	86 (65)		0.51	0.26-1.00	0.05
%Day 1-7 of CRRT Requiring Vasoactives	50 (13-100)	38 (0-76)	0.006*	1.01	1.00-1.02	0.007
Median Fluid Balance Day 1-7, ml/kg/day	-4 (-13,3)	-7 (-16,4)	0.087*	1.0	1.0-1.0	0.81

Conclusions

- Septic children requiring CRRT have unique clinical characteristics and outcomes, including higher rates of MAKE 90 but lower 90-day RRT dependence, compared to those without sepsis. Despite these differences, there were no differences in how children with sepsis were prescribed CRRT compared to those without, representing an important area of further research.
- Duration and trend in vasoactive support early in CRRT course (the first 48 hours) appear to be prognostic (and potentially modifiable) risk factors for MAKE-90 in this population. Further prospective research is needed to investigate these findings.

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